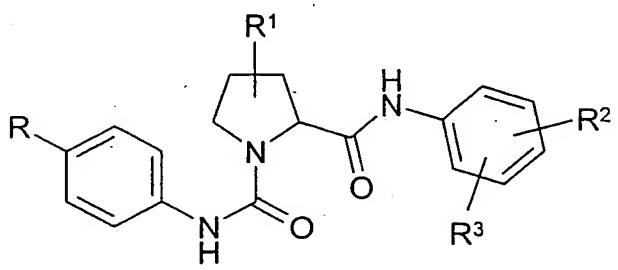
Patent Claims

1. Process for the preparation of compounds of the formula I



I

in which

R is Hal or C≡CH,

R^1 is H, =O, Hal, A, OH, OA, A-COO-, A-CONH-, A-CONA-, N_3, NH_2, NO_2, CN, COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$, O-allyl, O-propargyl, O-benzyl, =N-OH or =N-OA,

R^2 is H, Hal or A,

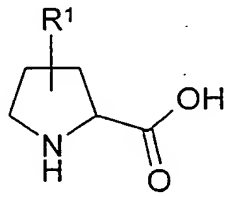
R^3 is 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2-oxo-1*H*-pyrazin-1-yl, 2-oxoimidazolidin-1-yl, 2-iminopiperidin-1-yl, 2-iminopyrrolidin-1-yl, 3-iminomorpholin-4-yl, 2-iminoimidazolidin-1-yl, 2-imino-1*H*-pyrazin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,6-dioxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl, 3-oxo-2*H*-pyridazin-2-yl, 2-caprolactam-1-yl (= 2-oxoazepan-1-yl), 2-azabicyclo[2.2.2]octan-3-on-2-yl, 5,6-dihydro-1*H*-pyrimidin-2-oxo-1-yl, 2-oxo-1,3-oxazinan-3-yl or 4*H*-1,4-oxazin-4-yl,
where the radicals may also be mono- or disubstituted by A or OA,

A is unbranched, branched or cyclic alkyl having 1-10 carbon atoms, in which, in addition, 1-7 H atoms may be replaced by F,

Hal is F, Cl, Br or I,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, characterised in that

a) a compound of the formula II

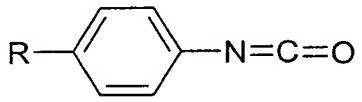


II

in which

R^1 is as defined above,

is reacted with a compound of the formula III

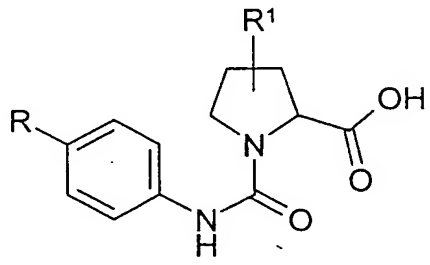


III

in which

R is as defined above,

to give a compound of the formula IV

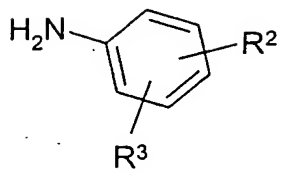


IV

in which

R and R^1 are as defined above,

b) a compound of the formula IV is then reacted with a compound of the formula V



V

in which R^2 and R^3 are as defined above,

to give a compound of the formula I, and

c) this is, if desired, converted into pharmaceutically usable derivatives and/or solvates thereof
by converting a base or acid of the formula I into one of its salts.

2. Process according to Claim 1 for the preparation of compounds of the formula I in which
R is F or Cl,
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

3. Process according to Claim 1 or 2 for the preparation of compounds of the formula I in which
R^1 is H, =O, OH, OA, A-COO-, N_3, NH_2, O-allyl or O-propargyl,
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

4. Process according to Claim 1, 2 or 3 for the preparation of compounds of the formula I in which
R^1 is H or OH,
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

5. Process according to one or more of Claims 1-4 for the preparation of compounds of the formula I in which

R^3 is 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2-oxo-1*H*-pyrazin-1-yl, 2-oxoimidazolidin-1-yl, 2-oxopiperazin-1-yl or 3-oxo-2*H*-pyridazin-2-yl,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

6. Process according to one or more of Claims 1-5 for the preparation of compounds of the formula I in which

A is unbranched or branched alkyl having 1-6 carbon atoms, in which, in addition, 1-3 H atoms may be replaced by F,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

7. Process according to one or more of Claims 1-6 for the preparation of compounds of the formula I in which

R is Hal or C≡CH,

R^1 is H, OH or OA,

R^2 is H, Hal or A,

R^3 is 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2-oxo-1*H*-pyrazin-1-yl, 2-oxoimidazolidin-1-yl, 2-oxopiperazin-1-yl or 3-oxo-2*H*-pyridazin-2-yl,

A is unbranched, branched or cyclic alkyl having 1-10 carbon atoms, in which, in addition, 1-7 H atoms may be replaced by F,

Hal is F, Cl, Br or I,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

8. Process according to one or more of Claims 1-7 for the preparation of compounds of the formula I in which

R is F or Cl,

R^1 is H, =O, OH, OA, A-COO-, N_3, NH_2, O-allyl or O-propargyl,

R^2 is H, F or A,

R^3 is 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2-oxo-1*H*-pyrazin-1-yl, 2-oxoimidazolidin-1-yl, 2-oxopiperazin-1-yl or 3-oxo-2*H*-pyridazin-2-yl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which, in addition, 1-3 H atoms may be replaced by F,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

9. Process according to one or more of Claims 1-8 for the preparation of compounds of the formula I in which

R is F or Cl,

R^1 is H or OH,

R^2 is H, F or A,

R^3 is 3-oxomorpholin-4-yl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which, in addition, 1-3 H atoms may be replaced by F,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

10. Process according to one or more of Claims 1-9, in which the reaction in step a) is carried out in an inert solvent or solvent mixture, in the presence of an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate.

11. Process according to one or more of Claims 1-10, in which the reaction in step a) is carried out in aqueous $NaHCO_3$ solution.

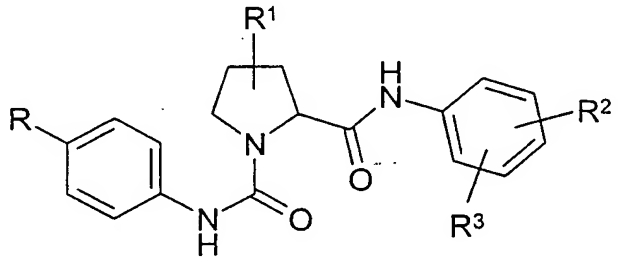
12. Process according to one or more of Claims 1-11, in which the reaction in step a) is carried out at a temperature between 60° and 110°C.

13. Process according to one or more of Claims 1-12, in which the reaction in step b) is carried out in the presence of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ).

14. Process according to one or more of Claims 1-13, in which the reaction in step b) is carried out at a temperature between 10° and 70°C.

15. Process according to one or more of Claims 1-14, in which the reaction in step b) is carried out in tetrahydrofuran.

16. Process according to one or more of Claims 1-15 for the preparation of compounds of the formula Ia



Ia

in which

R is F or Cl,

R^1 is H or OH,

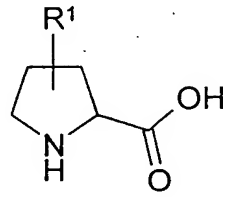
R^2 is H, F or A,

R^3 is 3-oxomorpholin-4-yl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which, in addition, 1-3 H atoms may be replaced by F,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, characterised in that

a) a compound of the formula II

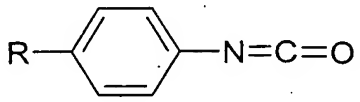


II

in which

R^1 is H or OH,

is reacted with a compound of the formula III



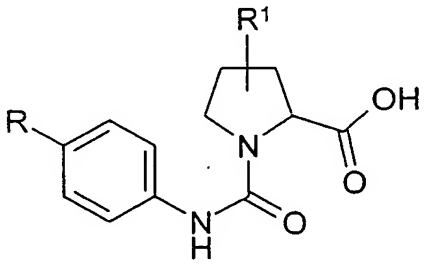
III

in which

R is F or Cl,

in aqueous alkali metal or alkaline earth metal carbonate or bicarbonate solution, at a temperature between 60° and 110°C,

to give a compound of the formula IV



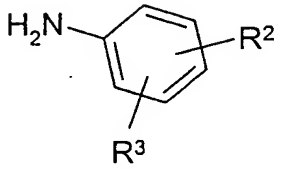
IV

in which

R is F or Cl,

R^1 is H or OH,

b) a compound of the formula IV is then reacted with a compound of the formula V



V

in which

R^2 is H, F or A,

R^3 is 3-oxomorpholin-4-yl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which, in addition, 1-3 H atoms may be replaced by F,

in the presence of an auxiliary reagent with formation of a mixed anhydride, at a temperature between 10° and 70°C,

to give a compound of the formula Ia, and

c) this is, if desired, converted into pharmaceutically usable derivatives and/or solvates thereof

by converting a base or acid of the formula Ia into one of its salts.

17. Process according to one or more of Claims 1-16 for the preparation of compounds selected from the group consisting of

1-[(4-chlor-phenyl)]-2-{[4-(3-oxo-morpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[3-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[3-trifluoromethyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-azidopyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-aminopyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-acetoxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R)-4-oxopyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2S)-pyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[3-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

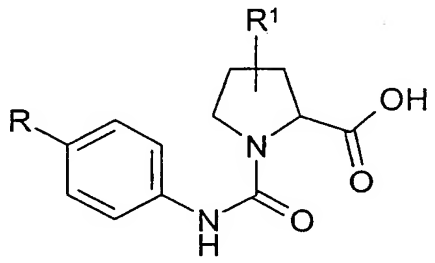
1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxamide,

1-[(4-chlorophenyl)]-2-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide.

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

18. Compounds of the formula IV



IV

in which

R is Hal or C≡CH,

R^1 is H, =O, Hal, A, OH, OA, A-COO-, A-CONH-, A-CONA-, N_3, NH_2, NO_2, CN, COOH, COOA, CONHA, $CONH_2$, $CON(A)_2$, O-allyl, O-propargyl, O-benzyl, =N-OH or =N-OA,

A is unbranched, branched or cyclic alkyl having 1-10 carbon atoms, in which, in addition, 1-7 H atoms may be replaced by F,

Hal is F, Cl, Br or I,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

19. Compounds according to Claim 18,

in which

R is F or Cl,

R^1 is H, =O, OH, OA, A-COO-, N_3, NH_2, O-allyl or O-propargyl,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

20. Compounds according to Claim 18 or 19,
in which
R is F or Cl,
R^1 is H or OH,
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.